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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/530,836	11/10/2005	Klaus Kopka	PZ0277	2454

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EXAMINER	
SCHLIENTZ, LEAH H	
ART UNIT	PAPER NUMBER
1618	
MAIL DATE	DELIVERY MODE
08/12/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/530,836	KOPKA ET AL.	
	Examiner	Art Unit	
	Leah Schlientz	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 June 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32* is/are pending in the application.

4a) Of the above claim(s) *3-7,17,19-25 and 30-32* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,8-16,18 and 26-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *08 April 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/8/2005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I in the reply filed on 6/1/2009 is acknowledged. The traversal is on the ground(s) that revised claims in which claim 1 has been amended such that a beta-emitter suitable for intravascular detection has been deleted from amended claim 1. Applicant asserts that the Examiner's non-unity rejection was based on the alleged disclosure in US 5,738,836 of a beta-emitting radionuclide conjugated to the 5-position of barbituric acid derivatives. Applicant asserts that Group 1 of amended claim 1 is also believed to make an inventive contribution over the prior art by providing imaging agents which permit in vivo imaging external to the mammalian body in a non-invasive manner, and this is believed represents a "special technical feature" which makes a contribution over the prior art.

This is not found persuasive. The common technical feature in all the groups is the imaging agent compound of claim1 including a barbituric acid matrix metalloproteinase inhibitor labeled at the 5 position of barbituric acid with an imaging moiety (i)-(vi). This element cannot be a "special technical feature" under PCT Rule 13.2 because the element is shown in the prior art.

US 3,952,091 teaches a gamma-emitting radioactive halogen (i.e. ^{125}I) conjugated to the 5 position of barbituric acid derivatives. See for example abstract, column 3, lines 9-11; column 5, line 65. As a result, no special technical features exist among the different groups because the invention in amended Group I fails to make a

contribution over the prior art with respect to novelty or inventive step. In conclusion, there is lack of unity of inventions, and therefore restriction for examination purposes as indicated is proper. The requirement is still deemed proper and is therefore made FINAL.

Applicant's election of compound 8 of Figure 1 including ^{18}F as imaging moiety, during a telephone conversation 8/4/2009, is also acknowledged.

Status of Claims

Claims 1-32 are pending, of which claims 30-32 are withdrawn as being drawn to a non-elected invention. Claims 3-7, 17, 19-25 are withdrawn as being drawn to non-elected species. Claims 1, 2, 8-16, 18 and 26-29 are readable upon the elected invention and are examined herein on the merits for patentability.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 2, 8-16, 18 and 26-29 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to an imaging agent which comprises a synthetic barbituric acid matrix metalloproteinase inhibitor labeled at the 5-position of the barbituric acid with an imaging moiety, wherein the imaging moiety can be detected following administration of said labeled synthetic

barbituric acid matrix metalloproteinase inhibitor to the mammalian body in vivo, and said imaging moiety is chosen from (i)-(vi). Dependent claims such as claims 9-14 define specific structures formula IV and V, having variables R^1 and R^2, including R", Z, Y, etc, which are specifically defined chemical moieties (e.g. H, C_{2-14} acyl, cycloaminoalkylene, etc as defined in the claims). The claims are confusing because dependent claims define specific compounds having specific variables, such as in claim 14 where R^1 is n-octyl, biphenyl, etc or C_6H_4-O-C_6H_4X, where X is H, C_{1-4} alkyl, Hal, OR, NR_2, etc., however, recitation of such specific moieties in position 5 of the barbituric acid do not identify the presence and position/location of the imaging agent claimed in the independent claim.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following references, drawn to non-elected species were found during the search for the elected species. It should not be interpreted that a comprehensive search was performed for all non-elected species.

Claims 1, 2, 15, 16, 18 and 26-28 are rejected under 35 U.S.C. 102(b) as being anticipated by Grunberg *et al.* (US 3,952,091).

Grunberg discloses a radiolabeled 5- or 5,5-substituted barbituric acid, i.e. secobarbital (abstract). In order to introduce ^{125}I, it may be necessary that the antigen molecule be derivatized preferably with a phenolic group which may be linked to the antigen by a C1-C5 alkylene linking group. Suitable derivatives include 5-allyl-5-[1-(p-hydroxyphenethyl-carbamyl)-2-propyl]barbituric acid useful as a secobarbital derivative (column 3, lines 1-10). See also column 5, line 65 drawn to the ^{125}I derivative of secobarbital, and claims 1-16. It is noted that the recitation of the intended use of the compound as an "imaging agent which comprises a barbituric acid matrix metalloproteinase inhibitor" has not been given patentable weight to distinguish over Grunberg because the intended use of the claimed invention must result in a structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). Since Grunberg discloses compounds having the structural features claimed (e.g. a barbituric acid moiety labeled at the 5-position) they would be capable of performing the intended use, as claimed. Regarding claims 26-28, the claims only require a non-radioactive

precursor "capable of" reaction with a positron emitting radioactive non-metal or gamma-emitting radioactive halogen.

Claims 1, 2, 9, 11, 15 and 26-28 are rejected under 35 U.S.C. 102(a) and (e) as being anticipated by Adamczyk *et al.* (US 6,472,227).

Adamczyk discloses tracers and immunogens made from substituted barbiturate compounds. A fluorescein moiety is included in the tracer (abstract). See Figures 5-8 comprising fluorescein conjugated to substituted barbituric acid derivatives at 5 position. It is noted that the recitation of the intended use of the compound as an "imaging agent which comprises a barbituric acid matrix metalloproteinase inhibitor" has not been given patentable weight to distinguish over Adamczyk because the intended use of the claimed invention must result in structural difference between the claimed invention and the prior art in order to patentably distinguish the claimed invention from the prior art. If the prior art structure is capable of performing the intended use, then it meets the claim. See *In re Casey*, 152 USPQ 235 (CCPA 1967) and *In re Otto*, 136 USPQ 458, 459 (CCPA 1963). Since Adamczyk discloses compounds having the structural features claimed (e.g. a barbituric acid moiety labeled at the 5-position with fluorescein) they would be capable of performing the intended use, as claimed. Regarding claims 26-28, the claims only require a non-radioactive precursor "capable of" reaction with a positron emitting radioactive non-metal or gamma-emitting radioactive halogen.

Claims 1, 2, 8, 15, 16, 18 and 26-28 are rejected under 35 U.S.C. 102(e) as being anticipated by Noe *et al.* (US 6,706,723).

Noe discloses pyrimidine-2,4,6-trione metalloproteinase inhibitors of formula ! wherein X, Y, A, B and R^1 are defined in the specification and pharmaceutical compositions and methods of treating inflammation, cancer and other disorders (abstract). See column 2-4 and 12-16 for various compounds, including several compounds fluorinated at 5-position of barbituric acid. The invention also includes isotopically labeled compounds which are identical to those recited in Formula I, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{18}F. Isotopically labeled compounds of Formula 1 can generally be prepared by carrying out the procedures disclosed in the schemes and/or examples and preparations, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent (column 20, lines 25+). Compositions include carriers and are sterile for parenteral administration (column 39, lines 55+).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the

> invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, 8-16, 18 and 26-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over Grams *et al.* (*Biol. Chem.*, 2001, 382, p. 1277-1285) in view of Noe (US 6,706,723), further in view of Carpenter *et al*. (US 6,656,448) and Mobashery *et al.* (US 6,703,415).

Grams discloses that matrix metalloproteinases (MMPs) are a family of zinc endopeptidases involved in tissue remodeling. They have also been implicated in various disease processes including tumor invasion and joint destruction. Therapeutic inhibition of one or several MMPs is therefore a promising approach e.g. for the treatment of arthritis or the prevention of metastasis. Matrix metalloproteases are attractive targets for inhibitor design (page 1277). New and promising lead structures for the inhibition of MMPs were identified, which can very probably also be used for other metalloproteases. The pyrimidine-2,4,6-triones we described bind to the MMPs in a manner that saturates nearly all possible interactions of the pyrimidine core moiety to the protein, besides the binding to the zinc, four hydrogen bonds are formed. A nearly perfect fit is obtained and there are even more interactions than seen with the typical

hydroxamates, where we find only three heteroatoms involved in binding. In addition to representing a very different new inhibitor class for MMPs, these compounds are also much more specific then most of the known MMP inhibitors currently under development (page 1282-1283). See Table 2 for compounds (example compounds 15, 16, etc.) and IC_{50} values for MMP-8, MMP-2 and MMP-9.

Grams does not specifically recite isotopically labeled pyrimidine-2,4,6-triones (barbituric acid derivatives), such as ^{18}F labeled structures for PET imaging.

Noe discloses pyrimidine-2,4,6-trione metalloproteinase inhibitors of formula ! wherein X, Y, A, B and R^1 are defined in the specification and pharmaceutical compositions and methods of treating inflammation, cancer and other disorders (abstract). See column 2-4 and 12-16 for compounds, including several compounds fluorinated at 5-position of barbituric acid. The invention also includes isotopically labeled compounds which are identical to those recited in Formula I, but for the fact that one or more atoms are replaced by an atom having an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes that can be incorporated include isotopes of hydrogen, carbon, nitrogen, oxygen, phosphorous, fluorine and chlorine, such as ^{18}F. Isotopically labeled compounds of Formula 1 can generally be prepared by carrying out the procedures disclosed in the schemes and/or examples and preparations, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent (column 20, lines 25+). Compositions include carriers and are sterile for parenteral administration (column 39, lines 55+).

Carpenter discloses imaging agents targeted to one or more MMP's would be very useful for detecting and monitoring the degree of extracellular matrix degradation in CHF, atherosclerosis and other degradative disease processes. These imaging agents, containing a ligand directed at one or more MMP's (e.g. MMP-1, MMP-2, MMP-3, MMP-9), will localize a diagnostic imaging probe to the site of pathology for the purpose of non-invasive imaging of these diseases. The imaging agent may be a MMP inhibitor linked to radioisotopes which are known to be useful for imaging by gamma scintigraphy or positron emission tomography (PET). Alternatively, the MMP targeting ligand could be bound to a single or multiple chelator moieties for attachment of one or more paramagnetic metal atoms, which would cause a local change in magnetic properties, such as relaxivity or susceptibility, at the site of tissue damage, which could then be imaged with magnetic resonance imaging systems. Alternatively, the MMP inhibitor can be bound to a phospholipid or polymer material which would be used to encapsulate/stabilize microspheres of gas which would be detectable by ultrasound imaging following localization at the site of tissue injury. Therefore, imaging agents based on MMP inhibitors would be extremely useful in the detection, staging and monitoring of cardiovascular diseases such as atherosclerosis (especially unstable arterial plaque) and various cardiomyopathies including congestive heart failure. Compounds of the present invention, which localize in areas of MMP activity in the heart, will allow detection and localization of these cardiac diseases which are associated with altered MMP levels relative to normal myocardial tissue. These imaging agents, whether for gamma scintigraphy, positron emission tomography, MRI,

ultrasound or x-ray image enhancement, have utility to detect and monitor changes in cardiovascular diseases over time (column). It is one objects of the invention to provide imaging agents for cardiovascular pathologies associated with extracellular matrix degradation, such as atherosclerosis, heart failure, and restenosis, comprised of matrix metalloproteinase inhibiting compounds conjugated to an imageable moiety, such as a gamma ray or positron emitting radioisotope, a magnetic resonance imaging contrast agent, an X-ray contrast agent, or an ultrasound contrast agent (column 1-4).

Mobashery discloses compounds that inhibit MMPs and methods of imaging tumor (abstract). Radiolabeled compounds of formula (I) are also useful as imaging agents for imaging cells comprising MMP's. Accordingly, the invention also provides compounds of formula (I) that include one or more detectable radionuclides (e.g., one or more metallic radionuclide and/or one or more non-metallic radionuclides). For example, a detectable radionuclide can be incorporated into a compound by replacing an atom of the compound of formula (I) with a radionuclide (e.g., non-metallic radionuclide). Alternatively, a radiolabeled compound of the invention can be prepared by linking a compound of formula (I) to a chelating group that includes a detectable radionuclide (e.g., metallic radionuclide). Such compounds can be useful to image tissues with MMP activity or tumors, in vivo or in vitro (column 12, lines 37+). Specifically, the non-metallic radionuclide can be a non-metallic paramagnetic atom (e.g., Fluorine-19); or a non-metallic positron emitting radionuclide (e.g., Carbon-11, Fluorine-18, Iodine-123, or Bromine-76) (column 13, line 43)

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide ^{18}F labels on the pyrimidine-2,4,6-trione metalloproteinase inhibitor compounds of Grams for the purpose of preparing imaging agents targeted to one or more MMP's, which would be very useful for detecting and monitoring the degree of extracellular matrix degradation in CHF, atherosclerosis and other degradative disease processes, as shown by Carpenter and Mobashery for other known MMP inhibitor compounds. One would have been motivated to do so because Carpenter and Mobashery teach that it is well known in the art to radiolabel MMP inhibitor compounds with radioisotopes which are known to be useful for imaging by positron emission tomography (PET), such as ^{18}F, for detection and localization of MMP and diseases associated therewith, and because Grams teaches that his compounds are more specific than other known MMP inhibitors. One would have had a reasonable expectation of success in doing so because Noe teaches that structurally similar pyrimidine-2,4,6-trione metalloproteinase inhibitors can be isotopically labeled, including using ^{18}F, which can generally be prepared by carrying out the procedures disclosed in the schemes and/or examples and preparations, by substituting a readily available isotopically labeled reagent for a non-isotopically labeled reagent.

Claim 29 is rejected under 35 U.S.C. 103(a) as being unpatentable over Grams *et al.* (*Biol. Chem.*, 2001, 382, p. 1277-1285) in view of Noe (US 6,706,723), further in view of Carpenter *et al.* (US 6,656,448) and Mobashery *et al.* (US 6,703,415), as

applied to claims 1, 2, 8-16, 18 and 26-28 above, in further view of Luthra *et al.* (US 7,115,249).

The rejection over Grams in view of Noe, Carpenter and Mobashery is maintained as above. It would have been further obvious to provide a kit for preparation of pyrimidine-2,4,6-trione radiopharmaceutical comprising precursor bound to solid support when the teachings of Grams, Noe, Carpenter and Mobashery are taken in view of Luthra.

Luthra discloses solid-phase processes for the production of radiolabelled tracers, in particular for the production of ^{18}F-labelled 6-L-fluorodopa which may be suitable for use as a PET tracer. The favoured isotope for PET, ^{18}F, has a relatively short half-life of 110 minutes. ^{18}F-labelled tracers, such as 6-L^{18}F-fluorodopa (6-^{18}F-fluoro-3,4-dihydroxy-L-phenylalanine) (^{18}F-FDOPA), for PET therefore have to be synthesised and purified as rapidly as possible and shortly before clinical use. Standard synthetic methods for introducing fluorine-18 are relatively slow and require post-reaction purification (for example, by HPLC) which means that it is difficult to obtain the ^{18}F-labelled tracer for clinical use in good radiochemical yield. The present invention provides solid-phase processes for producing ^{18}F-labelled tracers quickly yet avoiding time-consuming purification steps, such that the resultant ^{18}F-labelled tracer is suitable for use in PET. The solid-phase methods also lend themselves to automation with advantages of ease of production and greater throughput. The invention also comprises radiopharmaceutical kits which use such processes and thus provide

the radiopharmacist or clinician with a convenient means of preparing an ^{18}F-labelled tracer (see column 1 and examples).

It would have been obvious to one of ordinary skill in the art at the time of the invention to provide the compounds of Gram as precursors to ^{18}F radiopharmaceuticals bound to solid resin, and one would have been motivated to do so because Luthra teaches the advantages of solid phase synthesis of ^{18}F-labeled tracers such as rapid synthesis and ease of labeled product separation.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Leah Schlientz whose telephone number is 571-272-9928. The examiner can normally be reached on Monday - Friday 8 AM - 5 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Michael G. Hartley/
Supervisory Patent Examiner, Art Unit 1618

LHS